Title: Dyskeratosis Congenita *GeneReview* Supplemental Material **–** Less Common Genetic Causes

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Less Common Genetic Causes – from Table 1b

ACD

Gene structure. *ACD* consists of 12 exons on chromosome 16q22.1 (NM_001082486.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Two variants in *ACD* have been associated with disease [Guo et al 2014, Kocak et al 2014].

Table 7. *ACD* Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	ReferenceSequences
c.508_510delAAG	p.Lys170del	NM_001082486.1
c.1471C>A	p.Pro491Thr	NP_001075955.1

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The ACD (TPP1) protein is one of six proteins that bind to the telomeric DNA; their interactions with TIN2 and TERF2IP (RAP1) create a stable complex.

Abnormal gene product. Pathogenic variants in *ACD* result in loss of function of the TPP1 protein [Guo et al 2014, Kocak et al 2014].

NHP2 (*NOLA2*)

Gene structure. *NHP2* has four exons. NM_017838.3 is transcript variant 1, comprising 867 nucleotides. An alternative isoform lacks exon 3 (NM_001034833.1). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Three *NHP2* pathogenic variants (one homozygous and two as compound heterozygous changes) have been described in two affected individuals to date [Vulliamy et al 2008]. All were in exon 4.

Table 8. Selected Pathogenic Variants of *NHP2* (*NOLA2*) — Autosomal Recessive

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences	Literature Reference
c.376G>A	p.Val126Met	NM_017838.3 NP_060308.1	Vulliamy et al [2008]
c.415T>C [1]	p.Tyr139His		
c.460T>A [1]	p.Ter154ArgextTer51		

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Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Compound heterozygous mutant alleles observed in one affected individual

Normal gene product. The H/ACA ribonucleoprotein complex subunit 2 protein comprises 153 amino acids.

Abnormal gene product. Pathogenic variants in *NHP2* reported in two families resulted in reduced levels of TERC and shortened telomeres.

NOP10 (*NOLA3*)

Gene structure. *NOP10* comprises two exons. The transcript has 552 base pairs. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. One family with a homozygous *NOP10* pathogenic variant, c.100C>T (p.Arg34Trp), in the affected individual has been described [Walne et al 2007].

Table 9. Selected Pathogenic Variant of *NOP10* (*NOLA3*) — Autosomal Recessive

DNA Nucleotide Change	Predicted Protein Change	Reference Sequence
c.100C>T	p.Arg34Trp	NM_018648.3 NP_061118.1

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *NOP10* encodes an H/ACA ribonucleoprotein complex subunit 3 protein that comprises 64 amino acids.

Abnormal gene product. The reported pathogenic variant resulted in reduced TERC levels and shortened telomeres.

PARN

Gene structure. *PARN* consists of 27 exons across ~195 kb of genomic sequence on chromosome 16p13 (NM_002582.3). For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Missense, nonsense, frameshift, and splice site variants in *PARN* have been associated with disease.

Normal gene product. *PARN* encodes a 3'-exoribonuclease important in mRNA decay. It contains 669 amino acids (NP_001127949)

Abnormal gene product. Missense variants affect PARN deadenylation function.

WRAP53 (*TCAB1*)

Gene structure. *WRAP53* comprises ten exons. Alternatively spliced transcript variants that differ only in the 5' UTR have been found for the gene. NM_018081.2 is the longest transcript; other variants encode the same protein [provided by RefSeq, Mar 2011]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic allelic variants. Compound heterozygous pathogenic variants in *WRAP53* have been associated with disease in two families [Zhong et al 2011].

Table 10. Selected Pathogenic Variants of *WRAP53*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.492C>A	p.Phe164Leu	NM_018081.2 NP_060551.2
c.1192C>T	p.Arg398Trp	
c.1126C>T	p.His376Tyr	
c.1303G>A	p.Gly435Arg	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *WRAP53* encodes the TCAB1 protein, which is required for the transportation of telomerase to Cajal bodies in the nucleus for assembly of the telomerase ribonucleoprotein complex.

Abnormal gene product. Compound heterozygous pathogenic variants in *WRAP53* result in loss of the TCAB1protein, from Cajal bodies and mislocalization of telomerase.

References

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